

# Carrageenan nasal spray may double the rate of recovery from coronavirus and influenza virus infections: re-analysis of randomized trial data

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Yellow colour is used to indicate the results that are shown in the main text

This supplement describes the extraction of common cold duration mortality data from figures 2 and 5 of the Koenighofer IPD meta-analysis [28], and the statistical analysis.

[28] Koenighofer M, Lion T, Bodenteich A, Prieschl-Grassauer E, Grassauer A, Unger H, Mueller CA, Fazekas T. Carrageenan nasal spray in virus confirmed common cold: individual patient data analysis of two randomized controlled trials. *Multidiscip Respir Med.* (2014) 9:57.

<https://doi.org/10.1186/2049-6958-9-57>

<http://www.ncbi.nlm.nih.gov/pmc/articles/pmc4236476>

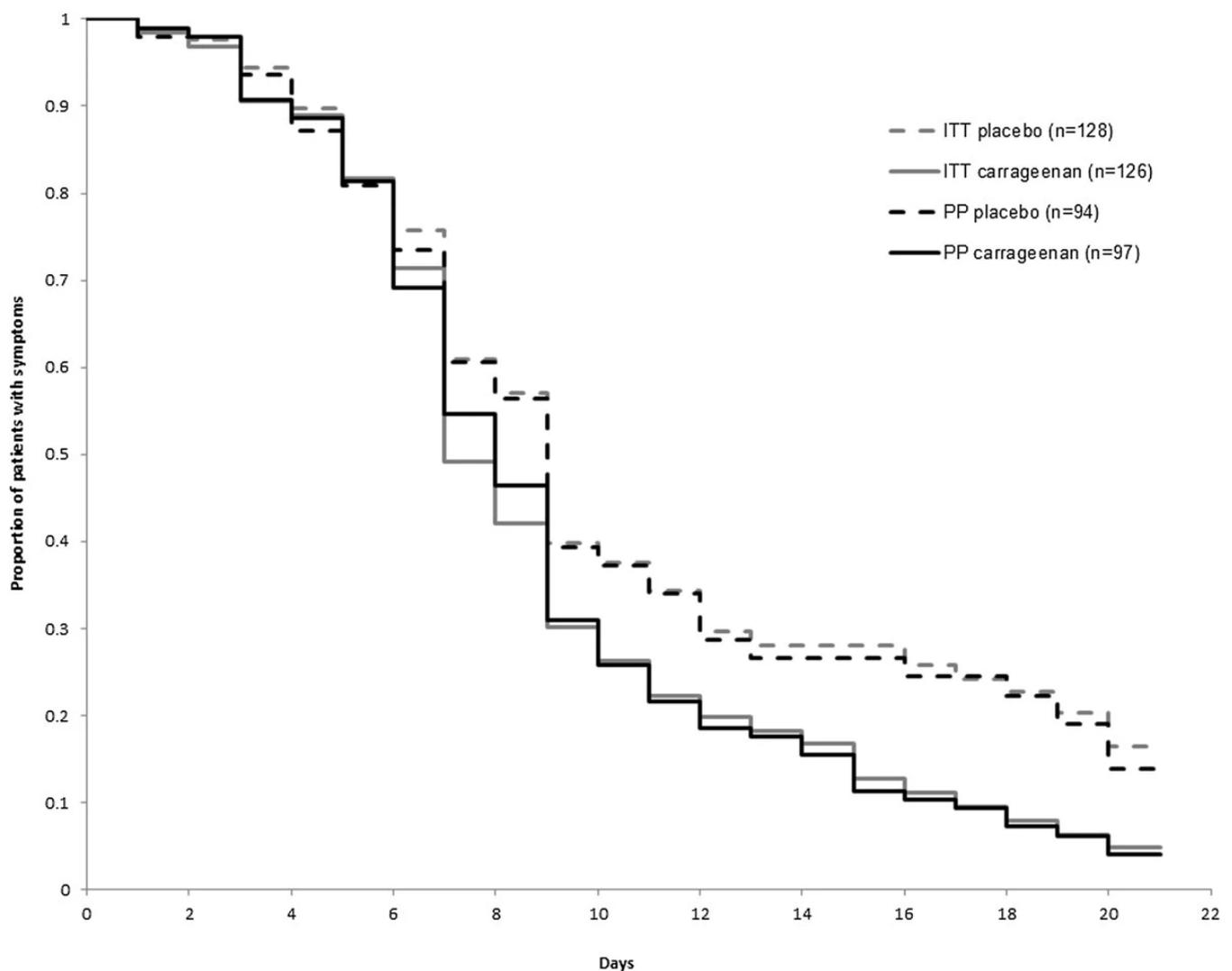
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## Extraction of data on common cold duration for all virus-positive colds

The recovery data in the IPD meta-analysis by Koenighofer [28] was published as survival curves. Their figure 2 for all virus-positive colds is copied below to illustrate the measurement of recovery over the follow-up period. Daily recovery is shown as steps in the survival curve. Both the ITT and per protocol analyses are shown in the original figure. Since the ITT analysis is generally preferable [30,31], we extracted the ITT data which is shown by gray in the figure.

When the number of patients is quite low, as in this case, it is possible to back-calculate from the survival curve the number of patients who recovered on each downward step. The size of the steps was measured from the digital figure as pixels and the scale of the figure as pixels was used to determine the number of recovered patients on each step. A spreadsheet was used to transform the pixel-values to the number of persons who recovered.

Similar approach was used to regenerate the data sets for the common cold episodes caused by coronaviruses, influenza A virus, and rhinoviruses which were published in figure 5 [28].



**Table 1: Recovery from the common cold by carrageenan administration (from figure 2 of Koenighofer (2014) [28])**

The left-hand side of this table shows the measurement of the steps in figure 2 [28].

The right-hand side shows the number of patients who recovered by the end of the given day.

The number of patients on each step can be inferred with great accuracy.

**All virus-positive colds, Figure 2 [28]**

Scale		Carrag		Placebo							
Still sick	pixels	N:	126		128						
100%	7										
0%	875										
gray:	line	dash	N cumulative		N of patients		N of patients				
			Calculated		on each step		on each step				
			Calculated		Calculated		Rounded to integers				
Day	Carrag	Placebo	Carrag		Placebo		Carrag		Placebo		Day
	pixels	pixels									
<b>0</b>	7	7	126.00	128.00	126.00	128.00	0	0	<b>0</b>		
<b>1</b>	20	20	124.11	126.08	-1.89	-1.92	2	2	<b>1</b>		
<b>2</b>	34	27	122.08	125.05	-2.03	-1.03	2	1	<b>2</b>		
<b>3</b>	88	54	114.24	121.07	-7.84	-3.98	8	4	<b>3</b>		
<b>4</b>	102	95	112.21	115.02	-2.03	-6.05	2	6	<b>4</b>		
<b>5</b>	165	169	103.06	104.11	-9.15	-10.91	9	11	<b>5</b>		
<b>6</b>	255	217	90.00	97.03	-13.06	-7.08	13	7	<b>6</b>		
<b>7</b>	448	346	61.98	78.01	-28.02	-19.02	28	19	<b>7</b>		
<b>8</b>	510	380	52.98	73.00	-9.00	-5.01	9	5	<b>8</b>		
<b>9</b>	613	529	38.03	51.02	-14.95	-21.97	15	22	<b>9</b>		
<b>10</b>	647	549	33.10	48.07	-4.94	-2.95	5	3	<b>10</b>		
<b>11</b>	681	576	28.16	44.09	-4.94	-3.98	5	4	<b>11</b>		
<b>12</b>	702	617	25.11	38.05	-3.05	-6.05	3	6	<b>12</b>		
<b>13</b>	716	631	23.08	35.98	-2.03	-2.06	2	2	<b>13</b>		
<b>14</b>	729	631	21.19	35.98	-1.89	0.00	2	0	<b>14</b>		
<b>15</b>	764	631	16.11	35.98	-5.08	0.00	5	0	<b>15</b>		
<b>16</b>	778	650	14.08	33.18	-2.03	-2.80	2	3	<b>16</b>		
<b>17</b>	793	664	11.90	31.12	-2.18	-2.06	2	2	<b>17</b>		
<b>18</b>	806	678	10.02	29.05	-1.89	-2.06	2	2	<b>18</b>		
<b>19</b>	820	698	7.98	26.10	-2.03	-2.95	2	3	<b>19</b>		
<b>20</b>	833	732	6.10	21.09	-1.89	-5.01	2	5	<b>20</b>		
<b>Cured by the end of day 20:</b>					119.90	106.91	120	107			
<b>Total not cured by day 20:</b>					6.10	21.09	6	21			
					<b>No recovery:</b>		<b>6</b>	<b>21</b>			
					<b>Total N</b>		126	128			
					<b>Quantile no recovery:</b>		0.952	0.836			

## Distribution of cold duration in all virus-positive patients by carrageenan administration

Total Observations in Table: 253

ALL\$Day	ALL\$Carrag		Row Total
	0	1	
1	2	2	4
2	1	2	3
3	4	8	12
4	6	2	8
5	11	9	20
6	7	13	20
7	19	28	47
8	5	9	14
9	22	15	37
10	3	5	8
11	4	5	9
12	6	3	9
13	2	2	4
14	0	2	2
15	0	5	5
16	3	2	5
17	2	2	4
18	2	2	4
19	3	2	5
20	25	8	33
Column Total	127	126	253

### Cox regression: all virus positive colds

```
> ALL_cox <- coxph(ALL_S ~ ALL$Carrag, method = "exact")
```

```
> summary(ALL_cox)
```

```
Call:
```

```
coxph(formula = ALL_S ~ ALL$Carrag, method = "exact")
```

```
n= 253, number of events= 227
```

	coef	exp(coef)	se(coef)	z	Pr(> z )
ALL\$Carrag	0.429	1.536	0.146	2.94	0.0033 **

	exp(coef)	exp(-coef)	lower .95	upper .95
ALL\$Carrag	1.54	0.651	1.15	2.05

```
Concordance= 0.543 (se = 0.02 )
```

```
Likelihood ratio test= 8.65 on 1 df, p=0.003
```

```
Wald test = 8.62 on 1 df, p=0.003
```

```
Score (logrank) test = 8.7 on 1 df, p=0.003
```

### Cox regression: two time periods of carrageenan effects

```
> TwoPeriods_Cox <- coxph(Surv(tstart, tstop, event) ~
```

```
Carrag:strata(tgroup), data=TwoPeriods, method = "efron")
```

```
> TwoPeriods_Cox
```

```
Call:
```

```
coxph(formula = Surv(tstart, tstop, event) ~ Carrag:strata(tgroup),  
      data = TwoPeriods, method = "efron")
```

	coef	exp(coef)	se(coef)	z	p
Carrag:strata(tgroup)tgroup=1	-0.02	0.98	0.29	-0.1	0.938
Carrag:strata(tgroup)tgroup=2	0.50	1.64	0.15	3.3	0.001

```
Likelihood ratio test=11 on 2 df, p=0.004
```

```
n= 459, number of events= 227
```

```
> exp(confint(TwoPeriods_Cox))
```

	2.5 %	97.5 %
Carrag:strata(tgroup)tgroup=1	0.552	1.73
Carrag:strata(tgroup)tgroup=2	1.221	2.21

**Distribution of cold duration in coronavirus OC43 and 229E patients by carrageenan administration,**

**Data from Eva Prieschl-Grassauer (2020-11-10)**

<b>Day</b>	<b>Carrag</b>	<b>Placebo</b>
<b>0</b>		
<b>1</b>	0	1
<b>2</b>	2	0
<b>3</b>	1	1
<b>4</b>	1	1
<b>5</b>	4	2
<b>6</b>	5	0
<b>7</b>	6	5
<b>8</b>	4	3
<b>9</b>	10	8
<b>10</b>	1	0
<b>11</b>	2	2
<b>12</b>	2	2
<b>13</b>	0	0
<b>14</b>	1	0
<b>15</b>	2	0
<b>16</b>	0	1
<b>17</b>	0	1
<b>18</b>	0	1
<b>19</b>	1	1
<b>20</b>	1	2
<b>Sums:</b>	43	31
<b>Total:</b>	45	43
<b>Not recovered:</b>	2	12

Total observations in Table: 88

hCV\$Day	hCV\$carrag		Row Total
	0	1	
1	1	0	1
2	0	2	2
3	1	1	2
4	1	1	2
5	2	4	6
6	0	5	5
7	5	6	11
8	3	4	7
9	8	10	18
10	0	1	1
11	2	2	4
12	2	2	4
14	0	1	1
15	0	2	2
16	1	0	1
17	1	0	1
18	1	0	1
19	1	1	2
20	14	3	17
Column Total	43	45	88

## Cox regression: coronavirus OC43 and 229E colds

```
> hcv_coxE <- coxph(hcv_S ~ hcv$Carrag, method = "exact")
> summary(hcv_coxE)
```

Call:

```
coxph(formula = hcv_S ~ hcv$Carrag, method = "exact")
```

n= 88, number of events= 74

	coef	exp(coef)	se(coef)	z	Pr(> z )	
hcv\$Carrag	0.8725	2.3929	0.2625	3.324	0.000886	***

---

	exp(coef)	exp(-coef)	lower .95	upper .95
hcv\$Carrag	2.393	0.4179	1.431	4.003

Concordance= 0.598 (se = 0.032 )

Likelihood ratio test= 11.3 on 1 df, p=8e-04

Wald test = 11.05 on 1 df, p=9e-04

Score (logrank) test = 11.48 on 1 df, p=7e-04

```
> lrtest(hcv_coxE)
```

Likelihood ratio test

Model 1: hcv\_S ~ hcv\$Carrag

Model 2: hcv\_S ~ 1

	#Df	LogLik	Df	Chisq	Pr(>Chisq)	
1	1	-192.92				
2	0	-198.57	-1	11.297	0.0007762	***

---



Total Observations in Table: 47

InfA\$Day	InfA\$Carrag		Row Total
	0	1	
1	0	1	1
2	0	1	1
3	1	2	3
4	1	1	2
5	1	1	2
6	2	2	4
7	3	3	6
8	1	2	3
9	4	2	6
10	1	1	2
11	0	1	1
12	1	0	1
14	0	2	2
15	0	2	2
16	1	1	2
17	1	0	1
20	7	1	8
Column Total	24	23	47

## Cox regression: influenza A colds

```
> InfA_cox <- coxph(InfA_S ~ InfA$Carrag, method = "exact")
> summary(InfA_cox)
```

Call:

```
coxph(formula = InfA_S ~ InfA$Carrag, method = "exact")
```

n= 47, number of events= 42

	coef	exp(coef)	se(coef)	z	Pr(> z )
InfA\$Carrag	0.785	2.192	0.343	2.29	0.022 *

---

	exp(coef)	exp(-coef)	lower .95	upper .95
InfA\$Carrag	2.19	0.456	1.12	4.29

Concordance= 0.582 (se = 0.043 )

Likelihood ratio test= 5.34 on 1 df, p=0.02

Wald test = 5.24 on 1 df, p=0.02

Score (logrank) test = 5.44 on 1 df, p=0.02

```
> lrtest(InfA_cox)
```

Likelihood ratio test

Model 1: InfA\_S ~ InfA\$Carrag

Model 2: InfA\_S ~ 1

	#Df	LogLik	Df	Chisq	Pr(>Chisq)
--	-----	--------	----	-------	------------

1	1	-104			
---	---	------	--	--	--

2	0	-106	-1	5.34	0.021 *
---	---	------	----	------	---------

**Distribution of cold duration in rhinovirus patients by carrageenan administration,  
Data from Eva Prieschl-Grassauer (2020-11-1)**

<b>Day</b>	<b>Carrag</b>	<b>Placebo</b>
<b>1</b>	1	2
<b>2</b>	0	1
<b>3</b>	7	2
<b>4</b>	2	4
<b>5</b>	5	7
<b>6</b>	6	6
<b>7</b>	18	11
<b>8</b>	3	2
<b>9</b>	7	13
<b>10</b>	4	3
<b>11</b>	2	2
<b>12</b>	0	4
<b>13</b>	2	2
<b>14</b>	1	0
<b>15</b>	3	0
<b>16</b>	1	1
<b>17</b>	2	2
<b>18</b>	2	1
<b>19</b>	1	2
<b>20</b>	0	1
<b>Sums:</b>	67	66
<b>Total:</b>	<b>70</b>	<b>80</b>
<b>Not recovered:</b>	3	14

Total observations in Table: 150

hRV\$Day	hRV\$Carrag		Row Total
	0	1	
1	2	1	3
2	1	0	1
3	2	7	9
4	4	2	6
5	7	5	12
6	6	6	12
7	11	18	29
8	2	3	5
9	13	7	20
10	3	4	7
11	2	2	4
12	4	0	4
13	2	2	4
14	0	1	1
15	0	3	3
16	1	1	2
17	2	2	4
18	1	2	3
19	2	1	3
20	15	3	18
Column Total	80	70	150

## Cox regression: rhinovirus colds

```
> hrv_cox <- coxph(hrv_S ~ hrv$Carrag, method = "exact")
> summary(hrv_cox)
Call:
coxph(formula = hrv_S ~ hrv$Carrag, method = "exact")

n= 150, number of events= 128

              coef exp(coef) se(coef)      z Pr(>|z|)
hrv$Carrag 0.533      1.705    0.192 2.77  0.0056 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

              exp(coef) exp(-coef) lower .95 upper .95
hrv$Carrag      1.7      0.587      1.17      2.49

Concordance= 0.553 (se = 0.026 )
Likelihood ratio test= 7.68 on 1 df, p=0.006
Wald test              = 7.68 on 1 df, p=0.006
Score (logrank) test = 7.8 on 1 df, p=0.005

> lrtest(hrv_cox)
Likelihood ratio test

Model 1: hrv_S ~ hrv$Carrag
Model 2: hrv_S ~ 1
  #Df LogLik Df Chisq Pr(>Chisq)
1   1   -356
2   0   -360 -1  7.68   0.0056 **
```

## Quantile regression 95% CI for the 60<sup>th</sup> and 80<sup>th</sup> percentiles, the latter to Figure 2

```
> fit.crq=crq(ALL_S ~ ALL$Carrag, tau= 0.5, method="PengHuang")  
> summary.crq(fit.crq, c(0.6,0.8), alpha = .05, R = 1000)
```

```
tau: [1] 0.6
```

Coefficients:

	Value	Lower Bd	Upper Bd	Std Error	T Value	Pr(> t )
(Intercept)	10.000	6.552	14.172	1.944	5.145	0.000
ALL\$Carrag	-1.000	-8.619	2.448	2.823	-0.354	0.723

```
tau: [1] 0.8
```

Number of NA Bootstrap Replications: 6 out of 1000

Coefficients:

	Value	Lower Bd	Upper Bd	Std Error	T Value	Pr(> t )
(Intercept)	20.000	16.552	20.000	0.880	22.740	0.000
ALL\$Carrag	-6.395	-10.567	-2.948	1.944	-3.290	0.001

## Risk ratio for the common cold to last over 20 days and the NNT

For the extraction of 6 and 21, see pages 2 and 3 of this supplement

```
> riskratio(6,21,126,128)
```

	Disease	Nondisease	Total
Exposed	6	120	126
Nonexposed	21	107	128

Risk ratio estimate and its significance probability

```
data: 6 21 126 128
```

```
p-value = 0.003
```

```
95 percent confidence interval:
```

```
0.121 0.695
```

```
sample estimates:
```

```
[1] 0.29
```

## Calculation of the NNT

```
>
```

```
> prop.test(c(6, 21),c(126, 128),correct=FALSE)
```

2-sample test for equality of proportions without continuity correction

```
data: c(6, 21) out of c(126, 128)
```

```
X-squared = 9, df = 1, p-value = 0.003
```

```
alternative hypothesis: two.sided
```

```
95 percent confidence interval:
```

```
-0.1906 -0.0423
```

```
sample estimates:
```

```
prop 1 prop 2
```

```
0.0476 0.1641
```

```
>
```

```
> (Difference = 0.16406250 - 0.04761905)
```

```
[1] 0.116
```

```
> (NNT = 1/Difference)
```

```
[1] 8.59
```

```
>
```

```
> # 95% CI for NNT
```

```
>
```

```
> (1/0.04229085)
```

```
[1] 23.6
```

```
> (1/0.19059605)
```

```
[1] 5.25
```

**Risk ratio for the lack of recurrence of cold symptoms**

Extraction of data

**figure 3 [28]**

<b>Relapses</b>	<b>Carrageenan</b>	<b>Placebo</b>	<b>RR</b>
ALL IPD			
N	126	128	
Reported %	13%	29%	
Relapses	16.38	37.12	
Rounded	16	37	0.44

**figure 6 [28]**

<b>Relapses</b>	<b>Carrageenan</b>	<b>Placebo</b>	<b>RR</b>
<b>hCV</b>			
N	45	43	
Reported %	18%	44%	
Relapses	8.1	18.92	
Rounded	8	19	0.40
<b>InfA</b>			
N	23	24	
Reported %	13%	38%	
Relapses	2.99	9.12	
Rounded	3	9	0.35
<b>hRV</b>			
N	70	80	
Reported %	9%	20%	
Relapses	6.3	16	
Rounded	6	16	0.43

```
> # ALL
> riskratio(16, 37, 126, 128)
      Disease Nondisease Total
Exposed      16         110   126
Nonexposed   37          91   128
```

Risk ratio estimate and its significance probability

```
data: 16 37 126 128
p-value = 0.002
95 percent confidence interval:
 0.258 0.748
sample estimates:
[1] 0.439
```

```
> # hCV
> riskratio(8, 19, 45, 43)
      Disease Nondisease Total
Exposed      8          37   45
Nonexposed   19         24   43
```

Risk ratio estimate and its significance probability

```
data: 8 19 45 43
p-value = 0.008
95 percent confidence interval:
 0.197 0.820
sample estimates:
[1] 0.402
```

```
> # Infa
> riskratio(3, 9, 23, 24)
      Disease Nondisease Total
Exposed      3          20   23
Nonexposed   9          15   24
```

Risk ratio estimate and its significance probability

```
data: 3 9 23 24
p-value = 0.057
95 percent confidence interval:
 0.10743 1.12612
sample estimates:
[1] 0.34783
```

```
> # hRV
> riskratio(6, 16, 70, 80)
      Disease Nondisease Total
Exposed      6          64   70
Nonexposed  16         64   80
```

Risk ratio estimate and its significance probability

```
data: 6 16 70 80
p-value = 0.049
95 percent confidence interval:
 0.17746 1.03503
sample estimates:
[1] 0.42857
```

## Calculation of the NNT for **the lack of recurrence** in the carrageenan patients

```
> prop.test(c(16, 37),c(126, 128),correct=FALSE)
```

2-sample test for equality of proportions without continuity correction

```
data: c(16, 37) out of c(126, 128)
X-squared = 10, df = 1, p-value = 0.001
alternative hypothesis: two.sided
95 percent confidence interval:
 -0.2598 -0.0644
sample estimates:
prop 1 prop 2
 0.127  0.289
```

```
>
> (Difference = 0.289 - 0.127)
[1] 0.162
> (NNT = 1/Difference)
[1] 6.17
>
> # 95% CI for NNT
>
> (1/0.2598)
[1] 3.85
> (1/0.0644)
[1] 15.5
```